DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region D1419B

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 331-2904

January 27, 1998

WARNING LETTER

RELEASE

REVIEWED BY _____ DATE
C.O.

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

John R. Stafford, President and CEO
American Home Products, Inc.
5 Giralda Farms
Madison, New Jersey 07940

FILE NO.: 98-NWJ-15

Dear Mr. Stafford:

During an inspection of your facility, Wyeth Ayerst-ESI Lederle, located at 2 Esterbrook Lane, Cherry Hill, New Jersey by the U.S. Food and Drug Administration between the dates of September 24 and November 14, 1997, our investigators documented serious deviations from the current good manufacturing practice (CGMP) regulations (Title 21, Code of Federal Regulations, Part 210 and 211) in conjunction with your firm's manufacture of prescription drug products.

These deviations were presented to your firm's attention on an FD-483 List of Observations at the close of the inspection on November 11, 1997. These CGMP deficiencies cause your products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

The significant observations are as follows:

1. Concurrent process validation studies for the manufacture of parenteral drug products are inadequate in that critical processing parameters have not been established. For example:

   A. Bulk holding times for non-sterile bulks prior to sterile filtration have not been established for the following marketed products: Amikacin, Aminocaproic, Atropine, Chlorpromazine, Cyanocobalamin, Diazepam, Digoxin, Diphenhydramine, Dopamine, Dopram, Dopram-V, Duramorph, Ephedrine, Furosemide, Gentamicin, Hep-Lock, Heparin, Hydromorphone, Isoproterenol, Lidocaine & Epinephrine, Lidocaine, Meperidine, Metronidazole, Morphine PCA, Naloxone, Neostigmine, Phenobarbital, Phenylephrine, Phenytoin, Procainamide, Prochlorperazine, Reglan, Robaxin-V, SMX-TMP, Sodium Chloride, Thiamine, and Water for Injection.

Additionally, bioburden and endotoxin testing was not performed on the non-sterile bulks during the concurrent validation studies.

B. Mixing times and filling line speeds have not been established for the products Hep-Lock, Gentamicin Sulfate, Diazepam Injection, and Bacteriostatic Sodium Chloride.

2. The Validation Report for Diazepam Injection, 5 mg/ml is incomplete in that the report did not discuss the failure of validation batch, Lot #026061, Diazepam Injection USP 1 ml fill in a 2.5 ml cartridge syringe, manufactured 2/26-27/96. Lot #026061 was rejected by the firm's Quality Assurance Department for low alcohol assay content.

3. Wyeth-Ayerst ESI Lederle has no process validation data available for the product Bacteriostatic NaCl Injection USP 0.9% 30 ml vial and 2.0/2.5 ml cartridge syringe.

Since 1994, the firm has released 67 lots of Bacteriostatic NaCl 30 ml vials and 26 lots of the 2 ml cartridge onto the market, without a validated manufacturing process. Most recent, Bacteriostatic NaCl 30 ml vial, Lot #09055 was released on 10/10/97.

4. The firm has no process validation data available for the product Dopamine 80 mg/ml, 5 ml vials.

Since 1994, [redacted] lots of Dopamine 80 mg/ml, 5 ml vials (Lot [redacted], [redacted] and [redacted] were released for distribution on [redacted], and [redacted].

5. The prospective validation studies for Atracurium Besylate Injection, 10 mg/ml, 6ml (unpreserved), and 10 ml vials are inadequate in that the established bulk holding time of [redacted] hours had not been challenged for bioburden, endotoxin, and chemistry, to demonstrate reproducibility.

6. The firm failed to follow product validation protocol [redacted] Rev.1, Atracurium Besylate Injection USP, 10 mg/ml, 5 ml fill/6 ml vial and 10 ml vial (Commercial Lot Validation) in that the protocol states that samples are to be collected and analyzed for all required tests. The protocol requires end of filling bulk tailing samples to be collected and tested for bulk chemistry, bioburden, and endotoxin for all batches. The firm tested only approximately [redacted] of the bulk tailing samples for bioburden and endotoxin and approximately [redacted] of the samples for bulk chemistry.

7. The prospective validation study for Sufentanil Citrate Injection USP, 0.05 mg/ml, 1 ml or 2 ml fill, 2 ml vial is inadequate in that the established bulk holding time of 24 hours was not challenged for bioburden, endotoxin, and chemistry, to demonstrate reproducibility.

8. The Quality Control (QC) Laboratory's "Instrument Calibration Procedure" SOP for the Perkin-Elmer 2S UV/VIS Spectrophotometer procedure #CP-014-00 is inadequate in that there is no evaluation of the instrument's photometric accuracy in the ultraviolet region. Additionally, there is no statistical assessment of linearity.

9. The QC Laboratory's "Instrument Calibration Procedure SOP #CP-045-00 for the HPLC Autoinjectors" is incomplete. The SOP does not adequately assess whether the instruments are operating according to specifications because linearity and accuracy are not assessed.

10. The QC Laboratory's "Instrument Calibration Procedure SOP #CP-019-00 for the Polarimeter" is inadequate in that it does not indicate the specific temperature that the standard and sample solutions under test must be maintained during specific rotation determinations.

We have received your response letter dated December 12, 1997, regarding the inspectional observation made on the FD-483. A preliminary review of your response shows that for many of the above listed observations you have initiated what appears to be appropriate corrective actions. We will confirm the adequacy of those corrective actions during our next FDA inspection.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the good manufacturing practice regulations. We request that you take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action without further notice. This includes seizure and/or injunction.

In addition, until the adequate corrective actions have been confirmed the Food and Drug Administration will not approve NDA's, ANDA's, or requests for evaluation by government procurement agencies which your firm may have pending involving drug products.

Any additional information you wish to submit should be sent to the Food and Drug Administration, New Jersey District Office, 10 Waterview Blvd, 3rd Floor, Parsippany, New Jersey 07054, Attention: Andrew Ciaccia, Compliance Officer.

We have agreed to your request for a meeting to discuss timeframes for completion of your proposed corrections. Please contact Andrew Ciaccia at (973) 331-2904 to schedule an appropriate time for the meeting.

Very truly yours,

Douglas Ellsworth

DOUGLAS ELLSWORTH
District Director
New Jersey District Office

AC:slw

cc: Dr. Ray Shaw
Vice President of Quality Assurance
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